## REMARKS

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1 and 3 are amended. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the present application. Claims 1-45 are pending.

*The 35 U.S.C. § 112, Second Paragraph, Rejections*

Claim 3, and claims 4-7, 15-17, 32-37, and 41-44 as they depend thereon, were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 10, and claims 4-7, 15-17, 32-37, and 41-44 "depending therefrom", were also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner asserts that it is not clear what codons are "preferentially" employed in a particular cell and how many codons are considered a "majority" in claim 3, and it is not clear what is considered "optimized" in claim 10. These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

Claim 3 is amended to recite that the codons are those which are preferentially employed in a mammalian host cell. It is Applicant's position that codons which are preferred in a particular host cell are known to the art (see, e.g., Wada et al., Nucl. Acids Res., 18:2367 (1990), cited on page 26 of the specification; of record). Therefore, the metes and bounds of the phrase "codons which are preferentially employed in a mammalian cell" in the claims is clear.

It is also Applicant's position that the term "majority" in claim 3 is clear, i.e., over 50% of the codons for a luciferase are modified.

It is unclear to Applicant's Representatives why claims 4-7, 15-17, 32-37 and 41-44 are rejected under § 112(2) for the term "optimized" (page 5 of the Office Action), when that term is only found in claim 10, claim 10 depends on claims 1 and 2, and only claims 30-31 depend on claim 10.

With regard to "optimized" nucleic acid sequences, it is Applicant's position that one of skill in the art is well aware of modifications that can optimize expression. See, for instance, Leclerc et al. (Biotechniques, 29:590 (2001)), Corish et al., Gilon et al. (EMBO J., 17:2759 (1998)) and Kastelic et al. (WO 00/36314), cited against the claims under 35 U.S.C. § 103(a); and WO 02/16944, cited at page 5 of the specification. Even if, assuming for the sake of argument, the metes and bounds of "optimized" nucleic acid sequences in claim 10 is not readily understood by one of skill in the art, Applicant's specification discloses exemplary optimizations, e.g., introduction of Kozak sequences, introduction of introns, and replacement of codons with codons preferred in a particular host, e.g., without introduction of transcription factor binding sites and other undesirable structural attributes (see pages 5 and 25 of the specification, and WO 02/16944). Hence, the metes and bounds of "optimized" in the claims is clear.

Accordingly, withdrawal of the § 112(2) rejections is respectfully requested.

*The 35 U.S.C. § 112, First Paragraph, Rejection*

Claims 1-11, 15-16, 18-20, 24-25, 30-32, 34-37, and 41-44 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the specification only describes polynucleotides having the nucleic acid sequence of SEQ ID NO:72, which encodes a fusion polypeptide comprising a specific luciferase, a specific PEST sequence, and a specific CL1, and as such does not constitute a representative number of species to describe polynucleotides encoding a fusion polypeptide comprising a whole genus of variants, recombinant and mutants of any or all reporter protein or luciferase and any or all protein and/or mRNA destabilization sequence or any or all PEST sequences. The Examiner also asserts there is no evidence on the record of the relationship between the structure of the polynucleotide of SEQ ID NO:72 and the structure of polynucleotide encoding a fusion polypeptide comprising any or all recombinant, variant and mutant reporter protein, protein and/or mRNA destabilization sequence or PEST sequences. This rejection is respectfully traversed.

Reporter proteins, protein destabilization sequences and mRNA destabilization sequences are known in the art (e.g., see Andreatta et al., Biotechniques, 30:656 (2001), Leclerc et al., Biotechniques, 29:590 (2001), Gilon et al., EMBO J., 17:2759 (1998), King et al., Mol. Biol.

Cell, 7:1343 (1996), Rechsteiner et al., Sem. Cell. Biol., 1:433 (1990), Fan et al., Genes and Devel., 11:2557 (1997), Balmer et al., Mol. Cell. Biol., 21:2070 (2001), and Belanger et al., Soc. Neurosci. Abs., 26:4117 (2000)) (all of record). Applicant need not describe what is known to the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94-95 (Fed. Cir. 1986).

Moreover, the specification discloses exemplary reporters, protein destabilization sequences and mRNA destabilization sequences at pages 5-6 and 23-24.

Further, the specification exemplifies three different firefly luciferase sequences (SEQ ID NOs:48-49 and 66), two different click beetle luciferase sequences (SEQ ID NOs:77 and 79), a *Renilla* luciferase sequence (SEQ ID NO:49), a green fluorescent protein sequence (SEQ ID NO:68), protein destabilization sequences (SEQ ID NOs:8-11, 13-15 and 46, which include mODC PEST sequences, CL1, optimized PEST sequences, optimized CL1 and PEST sequences with a UTR), and RNA destabilization sequences (SEQ ID NOs:3-6, including UTR and BLB RNA destabilization sequences) (see pages 5-6 and 23 of the specification). In addition, Applicant prepared and tested numerous constructs falling within the scope of the claims (see the Example).

To provide an adequate written description for a claimed genus, the specification can provide a sufficient description of a representative number of species by an actual reduction to practice, reduction to drawings or by a disclosure of relevant, identifying characteristics, i.e., by a structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics (Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099 (2001)).

As discussed above, Applicant has described a representative number of species for the claimed genus.

The Examiner cites Regents Univ. Calif. v. Eli Lilly, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997) to support the written description rejection. In Regents Univ. Calif. v. Eli Lilly and Co., the Federal Circuit held a patent invalid that claimed a recombinant microorganism comprising a human insulin encoding cDNA because the specification at issue did not disclose the nucleotide sequence of the claimed cDNA. The court stated that when dealing with claims to genetic material, generic claims, without more, do not amount to an adequate written description

of the claimed genus because they do not "distinguish the claimed genus from others, except for by function." Univ. of Calif. v. Eli Lilly and Co., 43 U.S.P.Q.2d at 1406.

However, in contrast to the claims at issue in Regents Univ. Calif. v. Eli Lilly, Applicant discloses numerous sequences falling within the scope of the claimed genus.

Thus, withdrawal of the § 112(1) rejection is respectfully requested.

*The 35 U.S.C. § 102(b) Rejection*

Claims 1, 3-7, 10, 15, 20, 25, 32, 35-37, and 41-44 were rejected under 35 U.S.C. § 102(b) as being anticipated by Corish et al. (Protein Eng., 12:1035 (1999)). This rejection is respectfully traversed.

Corish et al. disclose a constructs having green fluorescent protein linked to a 27 amino acid sequence from murine ODC that contained a PEST sequence or a 116 residue fragment from cyclin B1 that contained a destruction box (CDB), or both. Notably, the presence of both sequences resulted in a protein having a half-life substantially the same as the protein with only the CDB sequence. In this regard, the Examiner is requested to consider Figure 2 in Corish et al.

Corish et al. do not teach or suggest an isolated nucleic acid molecule comprising a nucleic acid sequence encoding a fusion polypeptide comprising a reporter protein and at least two different heterologous protein destabilization sequences, which fusion polypeptide has a reduced half-life relative to a corresponding reporter protein which lacks the heterologous protein destabilization sequences or has a reduced half-life relative to each corresponding reporter protein which has one of the heterologous protein destabilization sequences.

Nor does Corish et al. teach or suggest an isolated nucleic acid molecule comprising a nucleic acid sequence comprising an open reading frame for a luciferase and at least one heterologous destabilization sequence, where a majority of codons in the open reading frame for the luciferase are codons which are preferentially employed in a mammalian host cell.

Accordingly, withdrawal of the § 102 rejection is respectfully requested.

*The 35 U.S.C. § 103 Rejection*

Claims 1-11, 15-20, 24-25, 30-32, 34-37, and 41-44 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Leclerc et al. (Biotechniques, 29:590 (2001)), Corish et al.,

Gilon et al. (EMBO J., 17:2759 (1998)) and Kastelic et al. (WO 00/36314). This rejection is respectfully traversed.

Leclerc et al. prepared a construct in which a coding sequence for a firefly luciferase was linked to a murine ornithine decarboxylase (mODC) coding sequence that includes a PEST sequence found near the C-terminal of mODC. It is disclosed that the PEST sequence in mODC corresponds to residues 423-450, and that residues 423-461 of mODC (modified by an amino acid substitution at two positions), i.e., the C-terminal residues of mODC, were fused to firefly luciferase sequences (see Figure 1).

The Examiner acknowledges that Leclerc et al. do not teach the use of combinations of protein destabilization sequences, or a polynucleotide with at least one mRNA destabilization sequence.

Corish et al. do not provide what is missing in Leclerc et al., as Corish et al. do not teach or suggest an isolated nucleic acid molecule comprising a nucleic acid sequence encoding a fusion polypeptide comprising a reporter protein and at least two different heterologous protein destabilization sequences, which fusion polypeptide has a reduced half-life relative to a corresponding reporter protein which lacks the heterologous protein destabilization sequences or has a reduced half-life relative to each corresponding reporter protein which has one of the heterologous protein destabilization sequences. Nor does Corish et al. teach or suggest an isolated nucleic acid molecule comprising a nucleic acid sequence comprising at least two heterologous destabilization sequences, where one of the heterologous destabilization sequences is a mRNA destabilization sequence and another is a heterologous protein destabilization sequence, or an isolated nucleic acid molecule comprising a nucleic acid sequence comprising an open reading frame for a luciferase and at least one heterologous destabilization sequence, where a majority of codons in the open reading frame for the luciferase are codons which are preferentially employed in a mammalian host cell. Nor does Corish et al. teach or suggest a construct with a mRNA destabilization sequence.

Gilon et al. do not provide what is missing in Leclerc et al. or Corish et al., as Gilon et al. do not teach or suggest the use of combinations of protein destabilization sequences that have complementing effects, the use of a mRNA destabilization sequence with a protein

destabilization sequence, or a codon optimized luciferase sequence with at least one destabilization sequence.

Kastelic et al. disclose mRNA destabilizing sequences and a polynucleotide comprising a reporter DNA and a mRNA destabilizing sequences.

Kastelic et al. do not supplement what is missing in Leclerc et al., Corish et al., and Gilon et al., as Kastelic et al. do not disclose or suggest the use of combinations of protein destabilization sequences that have complementing effects, the use of a mRNA destabilization sequence and a protein destabilization sequence, or a codon optimized luciferase sequence with at least one destabilization sequence.

The Examiner asserts that in combining the teachings of Leclerc et al., Corish et al., Gilon et al. and Kastelic et al., it would have been obvious to one having ordinary skill in the art to make a polynucleotide encoding a fusion protein comprising a firefly luciferase and one or more protein destabilization sequences, such as a PEST sequence and a CL1 sequence, and/or one or more mRNA destabilization sequence. The Examiner continues that one of ordinary skill in the art would have been motivated to use other protein destabilizing sequences such as the CL sequences of Gilon et al. or a cyclin destruction box sequence as taught by Corish et al. or one or more mRNA destabilization sequences of Kastelic et al. in conjunction with PEST sequence in order to further reduce the half life activity/expression of luciferase. The Examiner asserts that one of ordinary skill in the art would have had a reasonable expectation of success since Leclerc et al. teach reducing the half-life activity of a luciferase by using a PEST sequence, Corish et al. teach that a combination of two protein destabilization sequences decreases half-life of reporter protein more than using only one of the protein destabilizing sequences, Gilon et al. teach CL protein destabilizing sequences that can be used to destabilize proteins, and Kastelic et al. teach destabilizing reporter proteins using mRNA destabilizing sequences.

The Examiner is reminded that the Examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.3d (BNA) 1596, 1598 (Fed. Cir. 1988). The M.P.E.P. contains explicit direction to the Examiner that agrees with the court's holding in In re Fine:

> In order for the Examiner to establish a *prima facie* case of obviousness, three base criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one

> or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. M.P.E.P. § 2142 (citing In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d (BNA) 1438 (Fed. Cir. 1991)).

With respect to claim 1, the combination of the cited art does not disclose or suggest combining protein destabilization sequences so that the resulting fusion protein has a shorter half life than each of the fusion proteins that have only one of the two protein destabilization sequences. With respect to claims 2 and 3, the combination of the cited art does not disclose or suggest combining a mRNA destabilization sequence and a protein destabilization sequence, or preparing a codon optimized luciferase sequence with at least one destabilization sequence. Therefore, the cited art fails to teach or suggest all the claims limitations.

Moreover, with respect to claims 1 and 2, because Corish et al. did not achieve a complementing effect with two protein destabilization sequences, the combination of the cited art fails to provide the motivation and the reasonable expectation of success alleged by the Examiner for combining destabilization sequences, e.g., combining protein destabilization sequences so that the resulting fusion protein has a shorter half life than each of the fusion proteins that have only one of the two protein destabilization sequences.

Thus, withdrawal of the § 103 rejection is respectfully requested.

## CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 29th day of March 2007.

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